REMARKS

Telephone Interview of November 18, 2004

Applicants would like to thank Examiner Zeman for a telephone interview on November 18, 2004 to clarify the remaining rejections. Applicants representatives Barbara Gyure and Mathew Beaudet discussed with the Examiner about the 112, first paragraph; 112, second paragraph; and the 103 rejections. The participants also discussed amendments to claims 24 and 32.

Claim Rejection Under 35 U.S.C. §112, First Paragraph

The pending claims 24, 26, and 28-32 are rejected under 35 U.S.C. §112, First Paragraph, as alleged not being enabled. The Office Action maintains that the specification does not enable any person skilled in the art to use the invention commensurate in scope with these claims. In addition, the Office Action states that, while the specification discusses the testing of fractions and sub-fractions, it does not describe how the fractions and sub-fractions were used in the assay. The Office Action also states that the specification does not provide guidance as to which biological functions or biological activities should be tested or how the testing of the functions would result in identifying one or more components that reduce an excessive Th1 response. Finally, the Office Action states that the specification fails to teach how animal models (e.g., as recited in Table 1) are to be used in the claimed method, or how the results of the exemplified methods (e.g., in example 8) could be correlated with identifying one or more components that reduce an excessive Th1 response. The Examiner therefore concludes that the specification is only enabling for an *in vitro* method of determining which helminthic fractions or sub-fractions can affect the immune response in mice.

Applicants have amended claim 24 to recite a method of screening a helminthic parasite preparation for one or more components that reduce a Th1 immune response, said method comprising the steps of: (a) obtaining a helminthic parasite preparation; (b) producing a homogenate of said helminthic parasite preparation; (c) separating fractions of said homogenate; (d) assaying a fraction of said homogenate to determine whether said fraction decreases a Th1

immune response; wherein a decrease in a Th1 immune response is indicative of said fraction comprising one or more components that reduce said Th1 immune response; and (e) further fractionating said fraction of step (d) into sub-fractions and identifying a sub-fraction that reduces a Th1 immune response. Claim 24, as amended, does not recite the phrases "excessive" and "biological activity," and it contains an additional step (e) of further fractionating the fraction of step (d). The above amendment is supported in the original claim 24 and throughout the specification, e.g., on pages 8-9 and page 21 (line 21) to page 24 (line 22).

For example, page 8, the third paragraph, teaches the following:

> "The invention also encompasses a method of screening a helminthic parasite preparation for one or more components that reduce an excessive Th1 immune response, the method comprising the step of assaying a fraction of a helminthic parasite preparation to detect a biological activity that reduces an excessive Th1 immune response."

Page 9, the fifth and sixth paragraphs, further teaches:

> "As used herein, the term 'biological activity that reduces an excessive Th1 immune response' refers to an activity contained within a helminthic parasite preparation that may be detected by its ability to reduce a Th1 immune response or an indicator of a Th1 immune response in an assay measuring Th1 immune response or indicators of a Th1 immune response.
>
> As used herein, the term 'fractionating' refers to the process of dividing a helminthic homogenate or fraction of a homogenate into smaller sub-portions or fractions on the basis of some physical, chemical or biochemical property."

Pages 21 to 24 then provide more detailed teachings on how to determine Th1 immune response. Therefore, the specification provides adequate support for the amendment in step (d) of claim 24.

In addition, the specification also provides adequate support for the amendment in step (e) of claim 24. For example, page 8, the third last paragraph, of the specification teaches the following about further fractionating:

> "In another preferred embodiment, a fraction containing one or more components that reduce an excessive Th1 immune response is subjected to the further step of fractionating and assaying to identify a sub-fraction containing one or more

components that reduce an excessive Th1 immune response. It is also preferred that the further fractionating and assaying steps are repeated at least once."

As such, the amendments in claim 24 is fully supported in the specification. No new matter is added.

Also, Applicants have amended claim 32 to recite the method of claim 24 wherein said assaying comprises administering a fraction from step (c) to a mammal and detecting a Th1 response in said mammal as evidenced by an in vitro assay. The above amendment is supported in the specification as filed, e.g., on page 21 (line 21) to page 24 (line 22). No new matter is added.

With regard to the sufficiency of the disclosure related to how to use the fractions and sub-fractions in the claimed invention or in the assay, Applicants submit that iterative fractionation and testing of resulting fractions and sub-fractions for activity is a well-known and routine method for isolating the biologically active component(s) of a complex biological mixture, as stated in the declaration by Dr. Weinstock and Dr. Elliott. As the declaration states, it is well known in the art that the same assay can be used at each stage of a fractionation procedure to monitor which fraction(s) or sub-fraction(s) have the activity of interest. For example, when fractionating an enzyme-containing preparation, the same enzyme assay is most often used at each stage of the fractionation procedure to monitor which fraction(s) or sub-fraction(s) contains the activity. Exemplary references provided herewith (see Exhibits A-C) show that it was well known in the art that in fractionation procedures, the same assay for the activity of interest can be used at each iteration of the method – that is, one fractionates, assays the fractions for activity of interest, then uses fractions or sub-fractions identified as having the activity for the next fractionation step, after which the fractions or sub-fractions are tested for the activity of interest using the same activity assay. As stated in the declaration, although the ultimate goals of the cited reference were to purify various proteins, all references describe fractionation processes, which clearly establish a common fractionation practice in the art. In Palczewski et al. (1988, J. Biol. Chem 263: 14067-14073; Exhibit A), a retinal extract was fractionated over a DEAE cellulose column, and all eluted fractions were monitored for rhodopsin kinase activity with a kinase assay (e.g., see Figure 3); in Soubeyrand et al. (1997, J.

Biol. Chem. 272: 222-227; Exhibit B), multiple fractions were assayed for Phospholipase A2 activity whether or not the fraction contains Phospholipase A2 (e.g., see Figure 1); in Ostergaard et al. (1997, J. Biol. Chem. 272: 30009-30016; Exhibit C), multiple fractions and sub-fractions, whether containing GLDase or not, are routinely assayed for GLDase activity which led to the purification of GLDase (e.g., see Figure 1). Therefore, the references demonstrate how fractions can be routinely made and routinely assayed, e.g., by the same assay, during the fractionation process by one with ordinary skill in the art. This does not rule out the use of a different assay at any point, but it is most common that a single assay be used to monitor the purification for all steps.

The specification provides guidance on assays and determination of a Th1 immune response at a number of places, for example, page 21, line 21 to page 24, line 22 and in the Examples. Specifically, at page 22, line 3-4, IFN-γ, TNF-α and IgG2a are taught to characterize a Th1 response, whereas IL-4, IL-5, IgE and IgG1 are taught to typify a Th2 reaction. At page 22, lines 4-10 the specification teaches that serum can be assayed for cytokine and immunoglobulin concentrations, and that flow cytometry can be used to examine Fcγ3 expression on macrophages (Th1) and MHC Class II expression on B cells (Th2). Assays for the detection of cytokines by flow cytometry and ELISA are further described at page 22, line 17 to page 23, line 20. Isotype-specific immunoglobulin assays are described at page 23,line 21 to page 24, line 2. Additional assays to determine lymphocyte secretion of antibodies or cytokines are described at page 24, lines 3-26.

Therefore, one of skill in the art would know that any of the assays provided by the specification can be used to test not only fractions, but also sub-fractions of a helminthic parasite homogenate for a fraction or a sub-fraction that reduces a Th1 immune response. For example, one of skill in the art would know that the same assay can be used for fractions and sub-fractions.

With respect to the statement in the Office Action that the specification does not provide guidance as to which biological functions or biological activities should be tested or how the testing of the functions would result in identifying one or more components that reduce an excessive Th1 response, Applicants submit that claims, as amended, no longer recite the phrase

"biological activity." The phrase "biological activity" is redundant in the claim language, as assaying for a decrease in a TH1 immune response is assaying for the presence of a biological activity. The amendment therefore obviates the rejections over "biological activity."

With respect to the Office Action's statement that the specification is only enabling for an *in vitro* method of determining which helminthic fractions or sub-fractions can affect the immune response in mice, Applicants submit that the specification is also enabling for an in vivo method.

With regard to assays performed *in vivo*, the specification provides guidance at page 30, line 23 to page 34, line 20, and in the Examples. More specifically, the specification teaches specific animal models for assaying the effect of a HH fraction or sub-fraction on a Th1 immune response in Table 1 (page 33-34), including animal models for Inflammatory Bowel Disease, Rheumatoid Arthritis, Insulin-Dependent Diabetes (type 1), Lupus , sarcoidosis, Multiple Sclerosis (MS), Autoimmune Thyroiditis, colon polyps/colon cancer and allergic airway diseases.

Example 8 provides details of the use of the mouse EAE model of MS to investigate the effect of schistosomes on autoimmune disease. The specification teaches in Example 8, page 48, lines 14-16 that "Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) involving autoimmune CD4+ helper T cells, particularly cells of the T helper 1 (Th1) subgroup." The use of the murine EAE mouse model of MS to investigate the effect of helminthic preparations on the Th1 response is also described at page 31, lines 4-8, which state that "Helminthic homogenate can be compounded with myelin basic protein (MBP) or PLP139-151 and mixed with CFA (adjuvant). SJL/J mice immunized with HH/MBP will develop no or greatly attenuated experimental autoimmune encephalomyelitis (EAE)." The parameters measured in Example 8 are described in the specification at page 28, lines 5, in the section titled "Multiple Sclerosis – Evaluation of Inflammation." This section describes criteria for clinical assessment of MS symptoms in the EAE mouse *in vivo* model. The criteria include motor function assessment, brain and spinal cord histology, and analysis of dispersed splenocytes

and cells from other regions. Applicants submit that this is an *in vivo* assay for the effect of helminthic components on a Th1 response.

Also with regard to guidance on *in vivo* assays and parameters to monitor, Example 3 provides details of the murine TNBS colitis *in vivo* model and its use to investigate the effect of schistosome infection on a Th1 immune response. The Example provides guidance regarding measurement of a Th1 response in mesenteric lymph nodes and spleen cells in response to T cell stimulation with anti-CD3 antibody (see page 40, lines 25-27, Table 2 (page 41) and Table 3 (page 42). Further guidance with regard to *in vivo* parameters to monitor is provided in Example 3 on page 42 where intestinal inflammation parameters are assessed on a 4 point scale – the scale is described at page 38, lines 309 in the section titled "Evaluation of Mucosal Inflammation." Applicants submit that this model is set forth with sufficient clarity to permit one of skill in the art to use it to monitor the effect of a fraction or sub-fraction of a helminthic homogenate.

The specification also teaches on page 31, lines 4-13, more specifically lines 4-5, that "[o]ther *in vivo* models exist that are useful for assaying helminthic homogenate or fractions of such homogenate for the ability to modulate an immune response." Specific *in vivo* models referred to in this paragraph include the EAE model discussed above and described in Example 8, the IL-10 -/- and TNBS treatment models for IBD (described in Example 3), and the NOD type 1 diabetes mouse model. The last sentence of this paragraph states that "Injections of HH may prevent any of the autoimmune or excessive inflammatory diseases listed in Table 1." That is, one would assay the effect of a fraction or sub-fraction of HH by injecting it into an animal that models disease and monitoring symptoms. It should also be noted that when performing *in vivo* experiments, one of ordinary skill in the art would routinely perform *in vitro* assays to confirm the *in vivo* observations. The fact that the specification teaches some *in vitro* experiments may be performed to confirm the *in vivo* observation is not evidence that the specification is not enabling for *in vivo* methods.

In view of this and the preceding discussion relating to the other points raised in the Office Action, Applicants submit that *in vivo* assays for assaying a fraction of a helminthic parasite homogenate for a fraction or a sub-fraction that reduces a Th1 immune response are

fully enabled, and respectfully request reconsideration and withdrawal of the enablement rejection of claims 24, 26 and 28-32.

Rejection under §103(a) over Pearce et al. (1991) in view of Pearce et al. (1988):

Claims 24, 26 and 28-32 are rejected under 35 U.S.C. §103(a) as obvious over Pearce et al. (J. Exp. Med. 173: 159-166, 1991) in view of Pearce et al. (P.N.A.S. 85: 5678-5682, 1988).

The Office Action states that Pearce et al. (1988) disclose a method of measuring various Th1 and Th2 hallmarks, the method identifies both Th1 enhancers as well as Th1 inhibitors. "Hence, the disclosed method comprises preparing and fractionating the preparation and assaying the products for the ability to reduce an excessive Th1 immune response. Moreover, Pearce et al. (1991) discloses that infected mice have a down regulation of Th1 responses (see page 164)." The Office Action states that Pearce et al. (1988) discloses a method of preparing antigens from *Schistosoma mansoni* that comprises obtaining adult schistosomes, homogenizing in phosphate buffered saline, centrifuging and purifying by immunoaffinity chromatography. The Examiner concludes that one of skill in the art would have been motivated to identify what stimulus was responsible and therefore, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare Schistosoma antigens utilizing the homogenization and immunoaffinity column chromatography disclosed by Pearce et al. (1988) and assay the resulting fractions for the ability to reduce excessive Th1 responses utilizing the assay methods disclosed by Pearce et al. (1991)." Applicants respectfully disagree.

Applicants submit that the independent claim 24, as amended, contains an additional step (e) of further fractionating said fraction of step (d) and identifying a sub-fraction that reduces a Th1 immune response. Neither Pearce et al. (1991), nor Pearce et al. (1988), nor their combination thereof, teaches a method containing an additional fractionation step which requires identifying a subfraction that reduces a TH1 immune response.

Applicants submit that Pearce et al. (1991) provides no motivation to screen a helminthic parasite preparation for one or more components that reduce a Th1 immune response by assaying a fraction to determine whether said fraction decreases a Th1 immune response and further

fractionating the fraction as claimed, because the reference focuses on the beneficial aspects of stimulating Th1 function -- the opposite result. The Abstract states "the data suggest that coincident with the induction of Th2 responses, murine schistosome infection results in an inhibition of potentially protective Th1 function." The reference also states "[t]hus, taken together, these previous studies suggest that infection stimulates a non-protective Th2-type response while vaccination induces protective Th1 cells" (p. 160, left column, first paragraph). Because the reference specifically refers to the Th1 response as "protective" and teaches that vaccination with Schistosome induces protective Th1 cells," there is no reason that one of skill in the art would be motivated to screen a helminthic parasite preparation for one or more components that *reduce* a Th1 response, as in the claimed invention.

The Pearce et al. 1991 reference teaches that "[i]n the mouse, infection with *Schistosoma mansoni* results in an egg-producing infection and associated disease, whereas vaccination with attenuated larval stages produces a substantial and specific immunity in the absence of egg-induced pathology." (Abstract) That is, egg-producing infection causes disease, and vaccination with attenuated larval stages provides protection from such infection, without the disease. Because the Th1 response described in the reference is associated with protective immunity from disease causing infection, one would not be motivated to further fractionate the fraction into sub-fractions and identifying a sub-fraction that reduces a Th1 immune response as claimed.

There is no recognition in either Pearce et al. reference that a Th1 immune response is something to be avoided. Thus, there is no reason that one skilled in the art, cognizant of the two Pearce et al. references, would screen a helminthic parasite preparation for one or more components that reduce a Th1 response by "assaying a fraction to determine whether said fraction decreases a Th1 immune response, as claimed," and further fractionating the fraction into sub-fractions and identifying a sub-fraction that reduces a Th1 immune response as claimed.

Applicants submit that the Pearce et al. (1988) reference cited does not alter the understanding of the Pearce et al. (1991) reference regarding the protective role of the Th1 response in immunity to *Schistosoma mansoni* infection. Therefore, one of skill in the art would not have been motivated by the teachings of Pearce et al. (1991) to screen a helminthic parasite

preparation for one or more components that reduce a Th1 immune response and further fractionate the fraction into sub-fractions and identifying a sub-fraction that reduces a Th1 immune response, as claimed. The combination of Pearce (1991) with the Pearce et al. (1988) reference would not suggest such a method. As such, Applicants submit that the claimed invention is not obvious over the combination of these references. Applicants respectfully request the withdrawal of the §103(a) rejection of claims 24, 26 and 28-32 over this combination of references.

Rejection under 35 U.S.C. §112, Second Paragraph:

Claim 32 is rejected as indefinite under 35 U.S.C. §112, second paragraph.

The Office Action states that claim 32 is indefinite because it omits the essential steps required for "detecting a Th1 response in said mammal."

Applicants have amended claim 32 to recite the method of claim 24 wherein said assaying comprises administering a fraction from step (c) to a mammal and detecting a Th1 response in said mammal as evidenced by an in vitro assay. The amended claim 32 clearly states that an in vitro assay is performed to detect a Th1 response in the mammal. Applicants submit that the amendment of claim 32 herein is sufficient to overcome this rejection. Applicants respectfully request reconsideration of the claim.

CONCLUSION

Claims 24, 26 and 28-32 are currently pending in the application. Claims 24, 26 and 32 are currently amended. The amendments find support in the specification and are discussed in the relevant sections above. No new matter is added.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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